REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1, 7, 11, 12, 13, 15, 18, 20, 22, 24, 28, 29 and 32-34 have been amended herein. Claim 1 has been amended to clarify the subject matter of step b). Claim 15 has been amended to remove the term "substantially". Claims 7, 11, 12, 13, 18, 20, 22, 24, 28, 29 and 32-34 have been amended to remove alternative language. The subject matter deleted herein from these claims has become the subject matter of new claims 60-84. Basis for these amendments may be found throughout the specification and claims as-filed, especially on page 22, line 31 to page 23, line 8. Thus, the amendments and new claims 60-84 do not introduce any prohibited new matter.

Applicants reserve the right to file a divisional or continuation application directed to any subject matter canceled by way of this Amendment.

Claim Objections

Claim 1 is objected to for the purported use of abbreviation and parenthesis in the recitation of "(PEG)". In the interest of expedited prosecution, claim 1 has been amended to delete "(PEG)", now reciting only "polyethylene glycol". Thus, Applicants respectfully submit that the objection to claim 1 has been obviated.

Claim Rejections under 35 U.S.C. § 112

Claims 1-37 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the application.

Claim 1 stands rejected for the recitation of the phrase "under such conditions that the biologically active substance is concentrated and/or solidified". The Office Action asserts that it is unclear what condition will cause the biologically active substance to be concentrated and/or solidified. Claims 3 and 5 stand rejected for the recitation of the phrase "highly viscous solution".

In order to clarify the subject matter which Applicants consider to be the claimed invention, independent claim 1 has been amended herein to recite, as step b), "concentrating the biologically active substance into a highly viscous solution thereof, which has the ability of forming droplets which can be handled at room temperature or into a precipitation thereof in the form of solid particles by mixing the solution obtained in step a) with an aqueous solution of polyethylene glycol". Applicants thus submit that it is clear as to what conditions causes the concentration of the biologically active substance and thus, the rejection is claim 1 is obviated.

Further, Applicants submit that this amendment to claim 1 obviates the rejections to dependent claims 3 and 5, as Applicants submit that the amendment clarifies that the term "highly viscous solution" refers to a solution capable of forming droplets which may be handled at room temperature.

Claim 4 stands rejected for the recitation of the phrase "reversibly solidified active substance". Applicants submit that the meaning of this term would be clear to the skilled artisan from review of the present specification. Specifically, Applicants refer the Examiner to page 24, second paragraph, of the specification, which defines a "reversibly solidified" active substance as a product which may be desolidified (dissolved) to the same chemical and biological form which it had held before.

Claim 15 stands rejected for the recitation of the phrase "starch is substantially lacking in covalently bonded extra chemical... found in hydroxyethyl starch". Claim 15 has been amended herein to remove the term "substantially" and to recite a starch that "lacks covalently bonded extra chemical groups which are found in hydroxyethyl starch". Thus, Applicants submit this rejection is obviated.

Claim 6 stands rejected for the recitation of the terms "400-1000,000 Da", "4000-35,000 Da", "6,000-20,000 Da", and "about 20,000 Da". Claim 7 stands rejected for the recitation of the terms "1-50% (w/w)", "2-45% (w/w)", "10-40% (w/w)", and "20-35% (w/w)". Claim 11 further stands rejected for the recitation of the terms "at most 10μg", and "at most 5μg". Claim 11 stands rejected for the recitation of the terms "exceeding 95% by weight" and "exceeding 98% by weight". Claim 13 stands rejected for the recitation of the terms "the range of 100-4,000 kDa", "200-1,000 kDa", and "300-600 kDa". Claim 18 stands rejected for the recitation of the terms "the range of 2.5-70 kDa", and "5-45 kDa". Claim 20 stands rejected for the recitation of the terms "at most 50% by weight", and "at most 45% by weight. Claim 22 stands rejected for the recitation of the

terms "at most 60°C", "at most 20-45°C", and "at most 30-37°C". Claim 24 stands rejected for the recitation of the terms "4-50°C", "10-40°C" and "10-37°C". Claim 28 stands rejected for the recitation of the terms "5-35 kDa", "15-25 kDa", and "ca. 20 kDa". Claim 29 stands rejected for the recitation of the terms "20-100μm" and "20-80μm". Claim 32 stands rejected for the recitation of the terms "1-20°C", "1-10°C", "around 4°C", "20-55°C", "25-40°C", and "around 37°C". Claim 33 stands rejected for the recitation of the terms "spray-drying... vacuum-drying", and "freeze-drying". Claim 34 stands rejected for the recitation of the terms "proteins... polysaccharides", and "recombinantly produced proteins".

In response, claims 7, 11, 12, 13, 18, 20, 22, 24, 28, 29 and 32-34 have been amended to remove alternative language. The subject matter deleted herein from these claims has become the subject matter of new claims 60-84. Thus, Applicants submit these rejections are obviated.

Rejections under 35 U.S.C. § 103

Claims 1-37 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Woiszwillo *et al.* (U.S. Patent No. 5,981,719), Ekman *et al.* (U.S. Patent No. 4,822,535) in view of Laakso *et al.* (*Journal of Pharmaceutical Sciences*, 75(10): 962-967 (1986)), and Takada *et al.* (U.S. Patent No. 5,622,657).

Woiszwillo *et al.* purportedly disclose a method of preparing biological active microparticles suitable for parenteral administration by mixing an aqueous solution of

bioactive compounds, such as insulin, leuprolide, and bovine Serum Albumin, with the solution of polyethylene glycol. Ekman *et al.* purportedly disclose a method to encapsulate bioactive substance in order to form solid microparticles by employing a two-phase emulsion system. Laakso *et al.* purportedly disclose polyacryl starch is suitable as carrier for passive target drug delivery since polyacryl starch is rapidly taken up by the reticuleondothelial system. Takada *et al.* purportedly disclose a prolonged release biological active microparticles which is coated by copolymers of polylactic/glycolic acid.

The Office Action states that it would have been obvious to the skilled artisan to prepare the claimed microparticles by employing the method of preparing microparticles by employing the method of Woiszwillo *et al.* followed by that of Ekman *et al.* The Office Action further argues that it would have been obvious to one of ordinary skill in the art to prepare the claimed microparticles by employing the method of Woiszwillo *et al* followed by that of Ekman *et al.*

Applicants ***traverse*** the rejection and assert that a *prima facie* case of obviousness has not been adduced. The test for obviousness is (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process, ***and*** (2) whether the prior art would have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success that it would work. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Thus, there must be both motivation to combine the reference and a reasonable expectation that the combination would work. The second prong of the test

also must be met for a *prima facie* obviousness determination. In the instant case, Applicants submit that there is neither a motivation to combine the references nor an expectation of success that the combination would work.

In the interest of expediting prosecution, claim 1 has been amended herein to further clarify and elucidate the concentration and solidification step of the claimed process. Specifically, claim 1 now recites a step of concentrating the biologically active substance into a highly viscous solution thereof, which has the ability of forming droplets which can be handled at room temperature or into a precipitation thereof in the form of solid particles by mixing the solution obtained in step a) with an aqueous solution of polyethylene glycol.

The primary reference cited herein is Woiswillo *et al.* Following the amendment of claim 1, Applicants submit that Woiszwillo *et al.* does not recite the elements of the claimed invention, or give the skilled artisan an expectation of success. Specifically, Woiszwillo *et al.* disclose microparticles containing an active substance with the objective of obtaining a stable slow release preparation. To accomplish this objective, Woiszwillo *et al.* use heat or chemical cross linking as a hardening step to impart the desired properties to the microparticles.

In contrast, the objective in the presently claimed invention is to convert a soluble biologically active substance, such as a protein, into a precipitate or highly viscous solution, for encapsulation in microparticles. This is accomplished by the use of an aqueous solution of polyethylene glycol. Thus, with regard to the presently claimed invention, the properties of the microparticles, not the solidified active substance, provides

the sustained release properties. The objective of the present invention of reversibly solidifying the active substance for encapsulation is different from Woiszwillo *et al.* Further, Woiszwillo *et al.* completely fails to recite the method of accomplishing the conversion of a soluble biologically active substance into a precipitate or highly viscous solution for encapsulation in microparticles

With regard to the secondary reference, Applicants submit that the disclosures do not remedy the deficiencies of the primary reference. Specifically, Ekman *et al.* merely disclose a method to encapsulate bioactive substances. Laakso *et al.* merely disclose that polyacryl starch is suitable as carrier. Takada *et al.* merely disclose a prolonged release biological active microparticles which is coated by copolymers. Thus, the skilled artisan would not combine these reference with the primary reference. Even if they did, they would not still arrive at the claimed invention.

Thus, there is no motivation to combine the references, there is not an expectation of success and the cited references do no recite all of the elements of the claimed invention, as amended herein. Thus, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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